Challenges to Human Subject Protections in US Medical Research

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United States regulations governing federally supported research with human subjects derive in part from 2 international codes, the Nuremberg Code and the Declaration of Helsinki. The Declaration of Helsinki states that "concern for the interests of the subject must always prevail over the interests of science and society." The concept of minimal risk and the principle of informed consent are the key means by which US federal regulations seek to protect the rights and welfare of the individual in the research setting. Current trends in medical research—including increased funding, ever-greater capabilities of computers, development of new clinical tools that can also be used in research, and new research tools developed through research itself—are creating greater demand for human subjects, for easier recruitment and conscription of these subjects, and for unimpeded access to patient medical records and human biological materials. Nationally and internationally, there are new pressures to subordinate the interests of the subject to those of science and society. The National Bioethics Advisory Commission, which is about to undertake a comprehensive review of the US system of human subject protections, faces a daunting task.

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EFFORTS ARE CURRENTLY WELL under way to alter both the US federal regulations and the international guidelines that govern or are intended to govern medical research. At the international level, both the Declaration of Helsinki[1] and the International Guidelines of the Council for International Organizations of Medical Sciences (CIOMS)[2] are under review.

In the United States, the National Bioethics Advisory Commission (NBAC), appointed by President Clinton in 1995, is charged with reviewing the US federal protections pertaining to human subjects research.[3] In addition, the US Office for Protection from Research Risks (OPRR) has intensified its activities in the last 2 years, scrutinizing more closely the practices of major research centers.[4,5] In 1998, OPRR revised for the first time since 1981 the federal regulations governing expedited review of research.[6,7] The principal focus of this article is on developments at the federal level.

HISTORICAL BACKGROUND

The US federal regulations that govern federally supported research with human subjects derive in part from 2 international codes promulgated after World War II in reaction to grossly unethical experimentation by Nazi physicians. These are the Nuremberg Code (1947)[8] and the Declaration of Helsinki (1964; since revised several times).[1] The first was the work of the US judges who tried the accused Nazi physicians, the second, the work of the World Medical Association. The Nuremberg Code has been called "the most important document in the history of the ethics of medical research,"[9] while the Declaration of Helsinki has been described as "the fundamental document in the field of ethics in biomedical research."[2(p9)]

There are differences in these codes, but they are alike in their insistence that patient autonomy be respected and supported and in their elevation of concern for the rights of individual patients and research subjects above scientific and societal goals. Adherence to the standards set by the Declaration of Helsinki is required by more than 500 medical journals in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."[10] This document instructs authors: "When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration. . . ."[10] The Declaration itself requires that "the research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with."[1]

The fifth and sixth principles in the Basic Principles section of the Declaration of Helsinki[1] spell out the perspective of the Declaration with respect to the appropriate relationship between individuals who serve as subjects in research and the goals of science and society. These principles read:

5. Every biomedical research project involving human subjects should be preceded by

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careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

A corollary of these principles is that "whether research results are important is immaterial in judging the ethics of the research."[11] That is, a study ought not to be judged ethical at its inception simply because it may produce useful results, and a study cannot become ethical ex post facto simply because it has produced useful results.

PRESSURES TO WEAKEN HUMAN SUBJECT PROTECTIONS

The concept of minimal risk and the principle of informed consent are the key means, although not the only ones, by which the US federal regulations pertaining to human subject research seek to protect the rights and welfare of the individual in the research setting. Yet the principle of consent "so unequivocally stated in the Nuremberg Code" is "diluted and deemphasized" in the existing federal regulations.[11] Current trends in research and research regulation continue to erode the requirement of consent, while the notion of minimal risk has become, as a commentator put it recently, "upwardly mobile."[12] These developments reflect a shift away from the underlying ethical framework of the Declaration of Helsinki, as expressed in the principles cited above.

These principles embody a point of view forcefully articulated by the philosopher and bioethicist Hans Jonas in a seminal article published in 1969.[13] "The physician," Jonas wrote, "is obligated to the patient and to no one else. He is not the agent of society, nor of the interests of medical science."[13] Jonas recognized that adherence to this stance might slow the march of medical progress but took the position that "progress is an optional goal" and that "its tempo in particular, compulsive as it has become, has nothing sacred about it."[13] The erosion of fundamental moral values seemed to Jonas to be a greater threat to society than slower progress in the conquest of disease and disability.

In recent years, however, in discussions regarding consent requirements, expedited review, medical privacy, genetic studies, research with the mentally ill, and other topics, it has become common to read or hear statements by medical researchers that assert the primacy of the interests of science and society and that place the burden of justification on those who would put any obstacles in the way of scientific and societal goals. These assertions are often accompanied by an unwillingness to admit that there are any true conflicts between the progress of science and the protection of human subjects.

For example, a recent NBAC report[14] concerning research involving persons with mental disorders that may affect decision-making capacity states: "Protecting human subjects from harm in research is perfectly compatible with pursuing important research goals; one does not have to be compromised to accommodate the other."[14(p8)] This sanguine assessment, however, is belied by the disagreements with respect to how to handle conflicts between subject protection and science facilitation that emerged during the drafting of this same NBAC report.

Particularly contentious was an NBAC recommendation that would permit a waiver of the consent requirement for research involving greater than minimal risk that includes a subject with impaired decision-making capacity and that does not offer the prospect of direct medical benefit to the subject. A waiver would be permitted under this recommendation if (1) a surrogate for the individual with impaired decision-making capacity grants permission for the individual's participation in the research and (2) a special panel of the US Department of Health and Human Services also grants permission, based on a finding that the research "offers the possibility of substantial benefit to the population under study," and that "its risks to subjects are reasonable in relation to this possible benefit."[14(pp54,61)]

In an addendum to the NBAC report, Alexander Capron, LLB, a member of the commission, observed that there is no way to avoid some measure of conflict between the pursuit of research and human subject protection. Capron, an advocate of strong human subject protections, noted that those "who favor placing some restrictions on research in the name of protecting subjects must recognize that we thereby deprive the populations of which those subjects are a part of any additional benefits unfettered research would provide beyond the benefits that can be achieved when more protective rules are followed."[14(p87)] The "heated protests"[14] (Capron's words) against certain protections recommended in the report, as well as the lobbying against more far-reaching protections that were not incorporated, indicate the reluctance of some to accept this cost.

It is the rapid march of science itself that is largely responsible for the pressures to weaken subject protections. Capability tends to be at odds with restraint. With respect to medical research, capability has expanded dramatically during the last 2 decades. Important factors are (1) the increase in available funds for medical research, (2) the vastly increased capabilities of computers, (3) the development of new clinical tools that can also be used for research (eg, imaging tools), and (4) the development of new research tools as an outcome of the research process itself (eg, the tools and techniques of microbiology). These increased capabilities are generating demands for ever-larger numbers of human subjects in research, for easier recruitment and conscription of research subjects, and for unimpeded access to patient medical records and human biological materials.

In his landmark 1966 article,[15] Henry Beecher, MD, then professor of research in anesthesia at Harvard Medical School, was already concerned about

growing expenditures for medical research. He commented, "Taking into account the sound and increasing emphasis of recent years that experimentation in man [sic] must precede general application of new procedures in therapy, plus the great sums of money available, there is reason to fear that these requirements and these resources may be greater than the supply of responsible investigators." In 1999 we have even more reason for concern, given increased federal and commercial funding of research activities.

INSTITUTIONAL REVIEW BOARDS

With respect to federally supported research, institutional review boards (IRBs) are designed to review and recommend modification, if needed, of research protocols, to reject irresponsible protocols, and to monitor ongoing projects. (The basic characteristics of the national IRB system are spelled out in the federal regulations concerning the protection of human subjects.[16,17]) The IRB system, however, has some inherent weaknesses and, at present, is overwhelmed by the quantity of protocols that are presented for review. In the last few years, the Advisory Committee on Human Radiation Experiments,[18] the Department of Health and Human Services' Office of the Inspector General,[19] and the US General Accounting Office[20] have each issued reports that questioned the capabilities of the IRB system. The inspector general's 1998 report states that "IRBs across the country are inundated with protocols" and that this "increased workload coupled with resource constraints, causes problems for IRBs and threatens the adequacy of their reviews."[19] According to the 1996 US General Accounting Office report, "In some cases the sheer number of studies necessitates that IRBs spend only 1 or 2 minutes of review per study."[20]

Efforts to fix the system, such as the recent revision of the categories of research eligible for expedited review (ie, review by as few as 1 member of an IRB) have produced controversial results.[21] Letters written by researchers and ethicists in reaction to the revisions proposed in 1997 by OPRR provide evidence of lack of agreement about the status of genetics research, use of magnetic resonance imaging and radiology in research, behavioral research on groups, research using videotapes and audiotapes of patients, research with children, and medical records reviews. (The 108 comments written in response to the proposed revision were obtained by the author from OPRR, pursuant to a Freedom of Information Act request dated July 11, 1998. These comments are also available for viewing at OPRR in Rockville, Md.)

The workload of IRBs is not the only factor that may affect the adequacy of review. Just as important is the way in which the standards set by the federal regulations are applied. A recent *US News & World Report* investigation describes numerous failures in this regard.[22] As noted above, the key subject protections in the regulations are (1) the requirement for informed consent, which is supposed to be obtained unless the conditions for a waiver are met, and (2) the minimal risk standard, which is supposed to protect subjects from incurring risks that are more than minimal if they have not consented and which is also used to rule out expedited review for research involving greater than minimal risk.

PROBLEMS DEFINING MINIMAL RISK

Minimal risk is defined in the federal regulations as a risk for which "the probability and magnitude of harm or discomfort anticipated . . . are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[23] However, there is substantial disagreement about what constitutes minimal risk, and the concept is applied quite variously. One group of commentators states: "'Minimal risk' seems to raise more questions than it solves. . . . There appears to be no natural or uniform understanding of 'minimal risk' upon which we can draw."[24] The recent NBAC report on research involving persons with mental disorders concurs: "The debate about the meaning of minimal risk will surely persist because of the philosophical and practical difficulties of defining it precisely."[14(p43)]

Other difficulties arise in the determination of risk because the IRB system is not designed to deal with the concatenation of the effects of research with human subjects or to permit comparative assessments of the decisions of different IRBs. There is no effective overview of the system or of the experiences of individuals or groups within the system. What looks like minimal risk to a local IRB may not appear that way in the context of the information generated by national research activities as a whole. Indeed, Gary Ellis, PhD, Director of OPRR, states that "the absence of comprehensive oversight permits systematic underestimation of risk by researchers" (oral communication, August 1999). When a minimal risk judgment is tied to a waiver of consent, participation in research rests on "substituted judgment," itself hazardous, because even "the most careful judgment regarding minimal risk cannot speak to the risk tolerance of an individual subject."[25]

MISJUDGMENTS AND DIFFERENCES IN INTERPRETATION OF RISK

Intensified oversight by OPRR has produced new evidence of misjudgment or misstatement of risk. In little more than a year, research activities have been restricted or suspended at 8 institutions. Among the most common complaints in the letters sent by OPRR to these institutions were failure to provide the safeguards required for the protection of vulnerable subjects and failure of investigators to accurately assess risks in consent forms (Gary Ellis, PhD, oral communication, August 1999. Copies of the letters sent to 4 of these institutions were obtained from OPRR pursuant to a Freedom of Information Act request dated August 5, 1999.) At 1 of these institutions, in a research project involving "hyperactive" and "normal" children, OPRR found that the "combination of all research procedures, including placement of an in-

dwelling intravenous catheter for serial blood drawing and administration of fluids, fenfluramine challenge, and genetic testing procedures" exceeded the limits of minimal risk and that, for the "normal" children in the control group, the research was impermissible under the federal regulations (letter from OPRR to Mount Sinai School of Medicine dated June 8, 1999).

The overall effects of misjudgments or misstatements of risk cannot be accurately assessed because, as noted above, there is no comprehensive system for compiling information regarding harm. Such assessment is also hampered by the fact that many IRBs are overwhelmed with adverse event reports and do not have the capability to review them carefully.[26(pp7-8)]

Researchers have strong incentives to seek minimal risk status for the research they propose to speed their work, since minimal risk research may obtain expedited review and waiver of consent requirements. The expanded list of categories of research eligible for expedited review published by OPRR in November 1998[6,7] reflects the pressure from researchers to make this list more inclusive and flexible. As noted above, it incorporates several categories about which there was disagreement in the public comments. For example, "one of the most controversial" involved "the use of human tissue and medical records."[21] Although the final list noted that confidentiality concerns and the risk of stigmatization must be taken into account in determining minimal risk status (a precondition of eligibility for expedited review), a number of writers argued that the determination of minimal risk in genetic studies and medical records research is sufficiently problematic that review by a full IRB (not just by 1 person or a subset of the IRB) ought to be required for these kinds of research.

INCONSISTENCIES, UNCERTAINTIES, AND DISAGREEMENTS ABOUT THE CONSENT REQUIREMENT

The consent requirement is currently subject to the same pressures as the minimal risk standard. The Declaration of Helsinki does not rule out altruism. The patient or potential subject may choose to make the ends of science his or her own. Ideally in such cases, the individual does not merely consent to participation in a research project but fully identifies with the ends of the project. (This is why surrogate consent raises troubling issues.) The dislike of some researchers for the consent requirement, which is the key to a research subject remaining a research subject rather than becoming a research object, is well known. The requirement is difficult to carry out properly and doing so may impede research. It may be regarded as an "unnecessary roadblock"[27] rather than as an opportunity for a useful and essential form of interaction with patients.

Under the existing federal regulations,[28] a waiver of the consent requirement can be granted if the risk is minimal, the rights and welfare of the subjects will not be adversely affected, and it is impracticable to get consent. A fourth condition requires that, whenever appropriate, subjects will be provided with pertinent information after participation in the research.[28] The waiver-of-consent provision dilutes the principle of consent as expressed in the Nuremberg Code and implicitly assumes that the consent requirement can be waived without necessarily violating a subject's rights. The application of these provisions has always been problematic. Given the difficulties of interpreting minimal risk, the application of the rights and welfare criteria in determining the appropriateness of a waiver is crucial. (This is clearly the case with research that undergoes expedited review, since minimal risk is already assumed.) But these criteria also suffer from difficulties of interpretation. In practice, IRBs may conflate the welfare criterion with the minimal risk criterion, while the rights criterion is given little attention, perhaps because of uncertainty about what a research subject's rights really are.[29(p38)] In fact, at several of the institutions found deficient by OPRR, IRBs had granted waivers of consent without finding and documenting the presence of the 4 criteria required by the regulations.

The NBAC has recently taken steps both to strengthen and to weaken the consent requirement. In its 1998 report on research involving persons with mental disorders,[14] the commission attempted to provide enhanced consent protection for persons with mental disorders by recommending that in general an "independent qualified professional" should assess the decision-making capacity of such subjects when they are included in research involving more than minimal risk. The commission had reviewed protocols for a number of recently published studies involving research of this kind, many including patients with serious psychiatric conditions. According to Alexander Capron, "Not a single protocol gave evidence of any effort on the part of the researchers to assess subjects' decision-making capacity."[30] Yet the commission's recommendation has provoked an outpouring of protest from psychiatric researchers. Curiously, this effort to protect psychiatric patients has been criticized as an attempt to "stigmatize" such patients,[31,32] rather than welcomed as a step that might lead to better protections for patients with other illnesses that may impair their decision-making capacity.

In contrast, a 1999 NBAC report on research involving human biological materials[29] proposes a weakening of the consent requirement, advocating in Recommendation 12 that the present federal regulations be changed so that IRBs (or in the case of expedited review, IRB chairpersons) can grant waivers of the consent requirement for studies involving identifiable, existing human biological materials, even where it *is* practicable to get consent—because what is practicable may not be convenient. In the words of the report, "Even in instances when it might be considered practicable to obtain consent for research use of stored biological materials, it may be burdensome for investigators to do so."[29(p69)]

This is a noteworthy departure for the commission, given that in 1997 it "resolved, as a matter of ethical principle, that no person should be en-

rolled in research without the twin protections of informed consent and independent review of the research."[33] Moreover, the recommendation is at odds with the rationale for the waiver-of-consent provision. The waiver provision was instituted because of the existence of situations of genuine impracticability and was designed solely for a subset of such situations.

Recommendation 12 is also surprising, given the difficulties in evaluating the risks of human biological materials research. The NBAC report[29] states with respect to genetics research and other "rapidly advancing fields" that "potential harms to individuals who are the subjects of such research are poorly understood and hence could be over- or underestimated. This is particularly true of nonphysical harms, which can occur in research conducted using previously collected human biological materials when investigators do not interact directly with the persons whose tissues, cells, or DNA they are studying."[29(p55)] In fact, in an earlier chapter, the report states: "In NBAC's judgment, where the research uses identified or coded samples from previously collected specimens, such uses are usually not justified without the source's consent, because the risks to sources and others may be more than minimal."[29(p48)] However, in the final chapter of this report, NBAC states (in Recommendation 10)[29(p68)] that studies that do not involve inappropriate release of information to the subject or to third parties may be considered minimal risk. On this point the commission errs, since a subject may validly object to and may suffer harm as a result of the pursuit and collection of information by the very party carrying out the study (whether governmental, commercial, or academic).

Given the commission's shifting opinions about the risk status of research with existing human biological materials, it might have recommended that such research, whether "minimal risk" or not, generally be carried out with unlinked (anonymized)[29(pp16-17)] materials if consent cannot be obtained, and it might have devised a new procedure for dealing with exceptional situations. The commission's recommendation to abolish the impracticability requirement for a waiver of consent with respect to this kind of research forfeits the opportunity for feedback from the subjects of such research in cases in which it is practicable to obtain consent and eliminates the necessity for IRBs to review the validity of impracticability claims for a whole class of studies.

The negative impact of Recommendation 12 may be compounded by the report's final recommendation (Recommendation 23), which urges that laws governing access to medical records be harmonized with rules governing research on human biological materials. The risks to subjects generally escalate when information obtained from human biological materials is linked to information in medical records. In combination with the decision by OPRR to permit expedited review of studies using existing and prospectively collected identifiable human biological specimens, these NBAC recommendations, if adopted, will contribute to a weak regime of protections with respect to genetic investigations, namely a regime in which a single individual is permitted to make the determination of minimal risk, evaluate the merits of a study, and grant waivers of consent (applying the new, lower waiver standards for studies using existing specimens).

MERGING CLINICAL PRACTICE AND MEDICAL RESEARCH

Adherence to the consent requirement is not a guarantee of ethical research. Research may violate what is ethically acceptable even when consent has been granted.[34] Yet the consent requirement is a particularly critical component of medical ethics, despite the difficulties that attend its application. A recent proposal to waive this requirement for certain randomized controlled trials generated strong criticisms,[35-40] in part because it would permit mingling the "fiduciary relationship between an individual patient and a physician" with the nonfiduciary relationship between a researcher and subject, without the patient or subject knowing that this had occurred.[35] Dissenters pointed out that the consent requirement relies on "the central bioethical principle of respect for persons,"[35] a fundamental precept in this country's bioethics tradition.

The NBAC is at a preliminary stage of its work with respect to the US system of protections for human research subjects. At its meeting on October 22, 1999, upon urging from the assistant to the president for science and technology policy, the commission decided unanimously to undertake a comprehensive review of the federal system of protections. The commission indicated an interest in recommending major structural changes.

In an earlier report on its preliminary findings, NBAC took note of the lack of comprehensive public accountability in the current, decentralized IRB system. The report also commented that "the absence of federal jurisdiction over much privately funded research means that the US government cannot know how many Americans currently are subjects in experiments, cannot influence how they have been recruited, cannot ensure that research subjects know and understand the risks they are undertaking, and cannot ascertain whether they have been harmed."[33(p1),41] It is important to keep in mind that some of these observations also hold true with respect to research that currently comes under federal regulation.

Whatever the result of NBAC's work, we must remain concerned about trends to subordinate subject protections to utilitarian efficiency, economic pressures, or governmental overreaching.[42] In a 1997 report to Congress, Donna Shalala, Secretary of the Department of Health and Human Services, stated that the usual requirement of patient consent for disclosure of personal medical records must give way to "our public responsibility to support national priorities—public health, research, quality care, and our fight against health care fraud and abuse."[43] Shalala's willingness to grant broad access to patient records occasioned protests in medical

journals and the news media.[44-47] At issue were not simply the risks that might be imposed on patients and medical personnel by such liberal disclosure policies, but Shalala's willingness to use bureaucratically designated "national priorities" as a rationale for overriding a traditional patient right and, potentially, patients' civil rights as well.

The subordination of human subject protections to "the interests of science and society"[1] may lead to a proliferation of greater than minimal risk investigations (frequently mislabeled as minimal risk), carried out without consent or with flawed consent procedures, and in some cases to harm that might have been avoided. A willingness to dilute protections for human subjects and a failure to respect individual autonomy in the research setting is likely to have a marked effect on the clinical setting as well.

The line between clinical practice and medical research is becoming increasingly blurred. The tools of medical investigation and of information gathering are being applied to human subjects with escalating intensity. The expansion of research using a variety of imaging and monitoring devices, human biological materials, and information processing technologies may, before long, turn every patient into a research subject (or rather, research object) simply by virtue of a decision to seek medical care. Assessing the broader implications of this trend for medical care and for society goes far beyond the assigned duties or competence of IRBs, which generally examine research only on an individual, project-by-project basis and whose members inadequately represent the interests of patients and the public.[48] A renewed commitment to safeguarding the integrity of the human subject will require new forums in which sustained attention can be given to these developments.

REFERENCES

1. World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *JAMA*. 1997;277:925-926.
2. International ethical guidelines for biomedical research involving human subjects. In: Bankowski Z, Levine R, eds. *Ethics and Research on Human Subjects: International Guidelines*. Geneva, Switzerland: Council for International Organizations of Medical Sciences; 1993.
3. Executive Order 12975 of October 3, 1995. Also available at http://www.bioethics.gov/about/eo12975.htm.
4. Hilts PJ. In tests on people, who watches the watchers? *New York Times*. May 25, 1999; Science Times: D1, D4.
5. Hamilton J. A watchdog's bite: quiescent for 26 years, the Office for Protection from Research Risks halts trials at three centers. *Physician's Weekly*. July 19, 1999;16(27):1.
6. 62 *Federal Register* 217 (November 10, 1997) 60607-60611.
7. 63 *Federal Register* 216 (November 9, 1998) 60364-60367.
8. The Nuremberg Code. *JAMA*. 1997;276:1691.
9. Shuster E. Fifty years later: the significance of the Nuremberg Code. *N Engl J Med*. 1997;337:1436-1440.
10. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals and Separate Statements. Available at: http://jama.ama-assn.org/info/auinst_req.html. Accessed October 6, 1999.
11. Angell M. Editorial responsibility: protecting human rights by restricting publication of unethical research. In: Annas GJ, Grodin MA, eds. *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*. New York, NY: Oxford University Press; 1992:278.
12. Mindling JD. A Catholic perspective. In: Shamoo AE, ed. *Conference Proceedings on "Research and Decisional Capacity."* Langhorn, Pa: Gordon & Breach Science Publishers. In press.
13. Jonas H. Philosophical reflections on experimenting with human subjects. *Daedalus*. 1969;98(2):219-247.
14. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity*. Vol. 1. Rockville, Md: National Bioethics Advisory Commission; 1998. Also available at http://www.bioethics.gov/pubs.html.
15. Beecher HK. Ethics and clinical research. *N Engl J Med*. 1966;274:1354-1360.
16. 56 *Federal Register* 117 (June 18, 1991) 28003-28032.
17. 45 CFR §46.
18. Advisory Committee on Human Radiation Experiments. *Final Report of the Advisory Committee on Human Radiation Experiments*. New York, NY: Oxford University Press; 1996.
19. Brown JG. *Institutional Review Boards: A Time for Reform*. Rockville, Md: Office of the Inspector General, US Dept of Health and Human Services; 1998. Publication OEI-01-97-00193.
20. Grob G. *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*. Washington, DC: General Accounting Office; 1996. Publication GAO/HEHS-96-72.
21. Campbell PW. US agencies seek to expand expedited reviews of research: officials see little risk to humans in certain studies. *The Chronicle of Higher Education*. April 3, 1998:A33.
22. Kaplan S, Brownlee S. Dying for a cure. *US News & World Report*. October 11, 1999:34-43.
23. 45 CFR §46:102(i)(1994).
24. Freedman B, Fuks A, Weijer C. In loco parentis: minimal risk as an ethical threshold for research upon children. *Hastings Cent Rep*. 1993;23(2):15.
25. Adams JG, Wegener J. Acting without asking: an ethical analysis of the Food and Drug Administration waiver of informed consent for emergency research. *Ann Emerg Med*. 1999;33:218-223.
26. Brown JG. *Institutional Review Boards: Their Role in Reviewing Approved Research*. Rockville, Md: Office of the Inspector General, US Dept of Health and Human Services; 1998. Publication OEI-01-97-00190.
27. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med*. 1999;340:804-807.
28. 45 CFR §46.116(d)(1994).
29. National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. Vol. 1. Rockville, Md: National Bioethics Advisory Commission; 1999. Also available at http://www.bioethics.gov/pubs.html.
30. Capron AM. Ethical and human-rights issues in research on mental disorders that may affect decisionmaking capacity. *N Engl J Med*. 1999;340:1430-1434.
31. Michels R. Are research ethics bad for our mental health? *N Engl J Med*. 1999;340:1427-1430.
32. Oldham JM, Halmowitz S, Delano SJ. Protection of persons with mental disorders from research risk: a response to the report of the National Bioethics Advisory Commission. *Arch Gen Psychiatry*. 1999;56:688-693.
33. NBAC Summary of Preliminary Findings: Adequacy of Federal Protections for Human Subjects in Research. Memorandum from Harold T. Shapiro, NBAC chair, to President Clinton; May 4, 1999. Also available at: http://bioethics.gov/news.html.
34. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med*. 1999;341:992-996.
35. Carome M. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:448-449.
36. Grodin MA. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:449.
37. Dresser R. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:449.
38. Silverman H. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:449.
39. King NM, Churchill LR. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:449-450.
40. Tenery RM Jr. Is informed consent always necessary for randomized, controlled trials [correspondence]? *N Engl J Med*. 1999;341:450.
41. Charo RA. Human subjects have it worse than guinea pigs. *Chronicle of Higher Education*. June 25, 1999:A64.
42. Brennan TA. Proposed revisions to the Declaration of Helsinki—will they weaken the ethical principles underlying human research? *N Engl J Med*. 1999; 341:527-531.
43. Testimony of Donna E. Shalala, Secretary, US Dept of Health and Human Services, before the Senate Committee on Labor and Human Resources, September 11, 1997.
44. Skolnick AA. Opposition to law officers having unfettered access to medical records. *JAMA*. 1998;279:257-259.
45. Flawed US proposals on patients' privacy [editorial]. *Lancet*. 1997;350:823.
46. Medical files, or fishbowls [editorial]? *Washington Post*. September 23, 1997:A16.
47. Trifling with medical privacy [editorial]. *New York Times*. September 11, 1997:A30.
48. Annas GJ. Good as gold. In: *Judging Medicine*. Clifton, NJ: Humana Press; 1988:325.